EXHIBIT "B"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Jonathan D. Glass

Serial No.: 10/671,360

Filed: September 25, 2003

Confirmation No.: 7114

Group Art Unit: 1654

Examiner: Christina Bradley

Docket No.: 820701-1015

For: Ketoamide Inhibitors in Chronic Nerve Disease

DECLARATION OF JONATHAN D. GLASS PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
Alexandria, Virginia 22313-1450

Sir,

I, **Jonathan D. Glass**, hereby declare that:

Education and Experience

1. I am a co-inventor of the 10/671,360 application (hereinafter "the '360 application").

2. I graduated from Middlebury College with a Bachelor of Arts (1979) and from the University of Vermont, College of Medicine with an M.D. in 1985, serving as a student fellow in the Department of Pathology in 1983. My postgraduate training includes an internship in internal medicine at the University of Maryland, Baltimore, MD, residency in neurology at the Johns Hopkins Hospital (serving as Chief Resident in Neurology from 1988 to 1989), and a postdoctoral research and clinical fellowship in the departments of Pathology and Neurology at The Johns Hopkins University, Baltimore, MD. I was a visiting research scientist in 1995 in the Department of Microbiology and Infectious Diseases at Flinders University, Bedford Park, South Australia. I hold a license in Medicine, as well as specialty boards in psychiatry and neurology with special

qualifications in clinical neurophysiology and I am also board-certified in neuropathology.

3. I am an inventor or co-inventor on 2 patent applications currently pending.

4. Since graduating with my M.D., I have been involved in a variety of pursuits related to the field of neurology, specifically the mechanisms of and the development of therapies for peripheral neuropathy. In addition to the postgraduate training mentioned above, I have held several academic, clinical, and professional appointments at various institutions including The Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, Emory University School of Medicine, Emory University Hospital, The Emory Clinic, Grady Hospital, and Wesley Woods Geriatric Hospital, and currently hold a tenured position at Emory University School of Medicine. I have held or currently hold memberships with several academic/scientific organizations including the American Neurological Association, The American Academy of Neurology, and the Society for Neuroscience. I also serve as a member or advisor for many institutional committees for Emory University, including the Hospital Neurophysiology Committee and as Director of the Neurology Residency Program. I serve on the editorial board for the scientific journal Experimental Neurology. I have also served as a reviewer for a number of other scientific journals, such as the American Journal of Neuroradiology, Annals of Neurology, Journal of Comparative Neurology, Journal of Neuropathology and Experimental Neurology, Journal of Neuroscience, Journal of Peripheral Nervous System, Neurology, and Neuroscience, among others. My research focus is on the mechanisms of axonal degeneration in models of peripheral neuropathy and the study and development of therapies for peripheral neuropathy, as well as the mechanisms and models in motor neuron diseases/ALS and the pathogenesis and pathological features of HIV-associated neurological diseases. I have been principle

investigator on several research grants, which have primarily been funded by the National Institutes of Health, but include other private foundations and industrial organizations. I also teach several courses at the Emory University School of Medicine in the medical school and graduate program and supervise residents and post-doctoral fellows. I have published over 75 research and review articles in scientific journals, have published several book chapters, have served as visiting professor and lecturer at numerous academic and research institutes, and have spoken at numerous national and international conferences and seminars.

5. Through my education and research in neurology and neuropathology, especially in the area of peripheral neuropathy, I have gained extensive experience in the field of axonal degeneration and peripheral neuropathy, specifically the mechanisms and inhibition of axonal degeneration associated with peripheral neuropathy.

The Office Action and Presently Pending Claims

6. I have reviewed the Office Action mailed on August 23, 2006 and understand that the presently pending claims stand rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Saatman *et al.* (Proc. Natl. Acad. Sci. USA, 93, 3428-3433 (1996)) (hereinafter, "Saatman") in view of Wang *et al.* (J. Neuropathology and Experimental Neurology, 59, 599-606 (2000)) (hereinafter "Wang") and Schaecher *et al.* (Neurochemical Research, 26, 731-737 (2001))(hereinafter "Schaecher").

7. I have been involved in the drafting of the '360 application and prosecution of the presently pending claims. Presently pending claim 1 is directed to a method of treating axonal degeneration of the peripheral nervous system in a patient by administering to the patient a therapeutically effective amount of a compound of the

formula M^1-AA^2-AA^1-CO-NR_3R_4 (as defined in the '360 application), which includes the compound Z-Leu-Abu-$(CH_2)_3$-4-morpholinyl (AK295).

8. I understand that the Office Action takes the position that the combined teachings of Saatman, Wang, and Schaecher render the claimed methods of treating axonal degeneration of the peripheral nervous system obvious to one of skill in the art.

Discussion

9. With respect to the Saatman reference, this reference deals with major trauma to the head, which is part of the central nervous system. Head injured animals exhibit major motor and cognitive dysfunction following injury. They experience loss of many types of neurological cells in the brain following the injury. In my opinion and based on my experience with the study and treatment of brain injuries and peripheral neuropathy and with the study of AK295, the effectiveness of AK295 in reducing the severity of the effects of the injury in the brain doesn't predict that AK295 would be effective in treatment of axonal degeneration in peripheral tissue during peripheral neuropathy (PN). PN results from injury to axons due to treatment with neurotoxic agents or due to diseases such as diabetes. It develops more slowly than a single traumatic injury to the central nervous system (CNS, i.e., brain and spinal cord). PN also more selectively affects axons and not the many types of tissues and cells injured in a head trauma. The experiments reported by Saatman describe protection against neuronal loss and not protection against axonal degeneration. Neuronal cell bodies are not the targets of the claimed methods for treatment of PN. The neuronal cell body and the axon are biologically separate structures that respond differently to nervous system injury (Coleman, M., Axon degeneration mechanisms: commonality amid diversity. Nat Rev Neurosci, 2005. 6(11): p. 889-98) (Attached hereto as Exhibit D). Thus, upon information and belief, one of skill in the art would understand both that the therapeutic

target of the claimed methods (axonal degeneration) is different than described by Saatman, and that her success in treatment of neuronal cell trauma does not predict that AK295 would be effective in treatment of axonal degeneration for peripheral neuropathy (PN).

10. With respect to the Wang reference, although the authors, which include myself, demonstrated the inhibitory effect of AK295 on axotomy and vincristine-induced axonal degeneration *in vitro*, it was still not obvious to those of skill in the art, including myself, that AK295 would provide effective inhibition in a whole animal model, even in view of the teachings of Saattman regarding the use of AK295 to treat mice with head trauma. First, evidence that a compound helps to treat one disorder (head trauma) does not lead to the conclusion that the compound will be useful to treat other disorders effected by different biological mechanisms (e.g., axonal degeneration associated with PN). Second, as understood by those of skill in the art, many compounds having *in vitro* activity do not have the same, if any, activity *in vivo*. Based upon this general knowledge and due to other factors and the skepticism of many of skill in the art (discussed in greater detail below) as to the *in vivo* activity of AK295 and its usefulness for treating axonal degeneration, we were doubtful of the potential success with AK295 for the in vivo treatment of axonal degeneration and almost abandoned testing of the compound.

11. Wang describes an *in vitro*, cell based models of vincristine neurotoxicity, but in spite of this teaching, my co-inventor and I were unable to develop a whole animal model of vincristine-induced neuropathy in order to test the hypothesis that AK295 would be useful for treatment of PN. We had to experimentally examine other neurotoxic agents until we found one that allowed the testing of AK295 in an animal model of PN.

12. Dr. Ray Bartus, who has extensive experience in the field of neurological diseases and their treatment and with AK295 and other calpain inhibitors (see the Declaration of Dr. Ray Bartus, Exhibit C), previously investigated AK295 for the treatment of stroke. I spoke to Dr. Bartus prior to beginning our experimental studies of AK295 in the mouse model of PN. In that conversation, Dr. Bartus expressed to me the opinion that our approach to protecting against axonal degeneration in PN by using AK295 "would not work" (See Exhibit C, paragraph 8). He expressed the belief that AK295 would not be orally active and that he did not think that it was possible to get AK295 into an animal in a therapeutically practical manner. This conversation almost prevented Dr. Powers and I from pursuing AK295 as a treatment for PN and conducting the animal experiments demonstrating that AK295 would be useful for treatment of PN.

13. Upon information and belief, no other investigators have pursued the use of AK295 for the treatment of PN in animals. AK295 has been available since 1994. Prior investigators thus had access to AK295, but were apparently unable to develop a method for treatment of PN based on the teachings of Saatman and Wang. Moreover, other calpain inhibitors such as calpastatin were readily available, and yet, upon information and belief, no one tried to use these to treat PN.

14. Peripheral neuropathies constitute a major category of neurological illness affecting millions of people worldwide. PN is a major dose-limiting complication of commonly used anti-cancer agents, including the Vinca alkyloids (vincristine, vinblastine), platinum-based drugs (cisplatin, carboplatin, oxaliplatin) and the taxanes (paclitaxel and Taxotere). In the case of paclitaxel (Taxol), data presented on a Gynecological Oncology Group (GOG) study at ASCO 2002 suggested that greater efficacy could be achieved if more cumulative Taxol was administered. These data suggest that drugs that mitigate PN (e.g., the calpain inhibitors of the '360 application) if used in combination with chemotherapy will likely result in

heightened efficacy of anti-cancer regimens because patients will be less likely to discontinue or reduce the dose of anti-cancer agents because of the complication of PN. PN is the most frequent neurotoxic side effect of drugs used for a wide spectrum of human diseases. In addition, common diseases such as diabetes mellitus, HIV infection, auto-immune disorders, and cancer are also frequently complicated by the onset and progression of debilitating peripheral neuropathies. The most common peripheral neuropathy in industrialized nations is diabetic polyneuropathy that may be present in up to 66% of type 1 diabetic patients and in nearly 59% of type 2 diabetic patients. Based on the foregoing and upon information and belief, there is an urgent need for a treatment for PN.

15. Upon information and belief, no treatments currently exist that prevent or repair the axonal degeneration that causes PN. The clinical management of axonal degeneration neuropathies is inadequate and is restricted to palliation of pain with analgesics and physical and occupational therapy for management of disability. No intervention, other than the removal of an offending toxic agent, has yet to demonstrate a significant therapeutic effect in axonal peripheral neuropathies. Other companies have tried to develop treatments for Peripheral Neuropathy, but they have thus far failed. A similar lack of success has been experienced in the fields of diabetic neuropathy and HIV neuropathy.

16. With respect to the Schaecher reference, although Schaecher suggests that calpain inhibitors may be used as "agents for the treatment of EAE", it does not indicate which, if any, available calpain inhibitors would be likely to work. Calpain inhibitors in general have been available for many years; however, upon information and belief, neither the authors of the Schaecher reference nor any others have demonstrated the effectiveness of the calpain inhibitor calpastatin or any other available calpain inhibitor in the treatment of EAE. Furthermore, protection against degeneration of

myelin proteins (as suggested in Schaecher et al.) is completely different than protection against degeneration of axons. The degeneration of myelin, the primary pathology in demyelinating diseases, is distinct from axonal degeneration, which is a secondary process in demyelinating diseases. Therefore, reduction or inhibition of one process does not necessarily affect the other. In my opinion, there is no logical connection between protection against immune-mediated demyelination in the central nervous system, as is seen in EAE, and protection against axonal degeneration, either in the case of multiple sclerosis or in any disorder of the central or peripheral nervous system. Therefore, based on the foregoing and upon information and belief, I submit that an inventive step was required to show that AK295, among other available calpain inhibitors in the literatures, was effective in animals for the treatment of axonal degeneration in EAE.

Conclusion

17. Based on the foregoing and upon information and belief, and further in view of the skepticism of experts in the field, the long-felt need in the art, and the general lack of alternative technologies, I submit that the claimed methods of treating axonal degeneration *in vivo* with AK295 or the other claimed compounds would not have been obvious to one of skill in the art knowledgeable of the combined teachings of Saatman and Wang.

18. Furthermore, upon information and belief, I submit that based solely on the teachings of Saatman and Wang, it would have taken extensive experimentation, with little likelihood of success, for one of skill in the art to achieve the claimed methods of the '360 application.

19. Based on the foregoing, and upon information and belief, I further submit that, based solely on the teachings of Saatman, Wang, and Schaecher, it would not

have been obvious to one skilled in the art to use AK295, among many other possible calpain inhibitors, for the *in vivo* treatment of axonal degeneration associated with EAE.

DECLARATION

I hereby declare that all statements made herein are of my own knowledge are true and that all statements are made on information and belief and are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Jonathan D. Glass M.D.

12-21-06
Date